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## **New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways**

Rogler, Gerhard ; Biedermann, Luc ; Scharl, Michael

**Abstract:** The exact pathophysiology of inflammatory bowel disease (IBD) is still unknown. However, over the years important insights allowed the development of novel therapeutic approaches that are at the threshold of introduction into clinical practice, or at least in clinical trials. After being first described by Burrill B. Crohn, Crohn's disease, one of the two major forms of IBD, was perceived as an infectious disease. When the concept of autoimmune diseases was formulated, Crohn's disease and ulcerative colitis were thought to be members of this disease group. T cells certainly contribute to the chronification of the intestinal inflammation and targeting T cell migration has been introduced some years ago as a successful therapeutic approach in IBD. Despite the development of successful therapy based on this pathophysiological concept, IBD is no longer seen as a typical autoimmune disease. After the millennium, genome wide association studies on genetic variants and risk factors in these polygenetic diseases have told us a lot about pathogenetic pathways. However, genetic susceptibility explains only up to one third of the cases. Environmental factors also must play a role. Those environmental factors may "transfer" their disease-promoting potential into pathophysiological pathways with the intestinal microbiota as mediator. Hence, the intestinal microbiota has gained much attention as an important factor in disease development. Microbial factors, as well as other direct environmental influences, have been shown to affect epigenetic signatures, intestinal epithelial cells and the innate immune system, providing another important concept on how these diseases originate and can cause repeated flares at the same gut segments even after years of remission and after intermediate complete mucosal healing. Current pathophysiological concepts of IBD not only help us to better understand these diseases and develop new therapies. They also illustrate the evolution of basic scientific concepts over time and that sometimes partially or even largely abandoned concepts persistently influence our current thinking/clinical practice.

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## New insights into the pathophysiology of inflammatory bowel disease: microbiota, epigenetics and common signalling pathways

Rogler Gerhard, Biedermann Luc, Scharl Michael

Department of Gastroenterology and Hepatology, University Hospital Zurich, University of Zurich, Switzerland

### Summary

The exact pathophysiology of inflammatory bowel disease (IBD) is still unknown. However, over the years important insights allowed the development of novel therapeutic approaches that are at the threshold of introduction into clinical practice, or at least in clinical trials. After being first described by Burrill B. Crohn, Crohn's disease, one of the two major forms of IBD, was perceived as an infectious disease. When the concept of autoimmune diseases was formulated, Crohn's disease and ulcerative colitis were thought to be members of this disease group. T cells certainly contribute to the chronification of the intestinal inflammation and targeting T cell migration has been introduced some years ago as a successful therapeutic approach in IBD. Despite the development of successful therapy based on this pathophysiological concept, IBD is no longer seen as a typical autoimmune disease. After the millennium, genome wide association studies on genetic variants and risk factors in these polygenetic diseases have told us a lot about pathogenetic pathways. However, genetic susceptibility explains only up to one third of the cases. Environmental factors also must play a role. Those environmental factors may "transfer" their disease-promoting potential into pathophysiological pathways with the intestinal microbiota as mediator. Hence, the intestinal microbiota has gained much attention as an important factor in disease development. Microbial factors, as well as other direct environmental influences, have been shown to affect epigenetic signatures, intestinal epithelial cells and the innate immune system, providing another important concept on how these diseases originate and can cause repeated flares at the same gut segments even after years of remission and after intermediate complete mucosal healing.

Current pathophysiological concepts of IBD not only help us to better understand these diseases and develop new therapies. They also illustrate the evolution of basic scientific concepts over time and that sometimes partially or even largely abandoned concepts persistently influence out current thinking/clinical practice.

**Key words:** inflammatory bowel disease, Crohn's disease, ulcerative colitis, pathophysiology, microbiota, epigenetics, T cells, environment

### Introduction

Inflammatory bowel diseases (IBDs) are chronic, relapsing inflammatory disorders of the intestinal tract usually starting in young adults and potentially causing a life-long burden and reduction of quality of life for the patients. There are approximately 12,000–15,000 adult cases in Switzerland. Data from the Swiss IBD cohort study (SIBDCS) suggest that (consistent with the majority of global epidemiological investigations [1]) the overall incidence is increasing [2]. Worldwide, over 2.5 million people of European ancestry are affected [3–7]. Increasingly, IBD is diagnosed in countries where it was almost absent 20 years ago, such as in Asia [8].

Crohn's disease may occur anywhere in the gut from the mouth to the anus. It is an often segmental but transmural inflammation of the gut wall. Inflammation in Crohn's disease may trigger fibrosis [9, 10] or fistula formation [11, 12]. Currently, despite recent advances in medical treatment options, up to 80% of the patients must undergo at least one surgical removal of an intestinal segment [13, 14]. In contrast, ulcerative colitis affects only the large bowel, always starting with highest activity in the rectum. It may be associated with high numbers of bloody bowel movements per day and has a huge impact on quality of life – up to 10 to 15% of patients will ultimately need colectomy [15, 16]. However, numbers seem to be decreasing.

Due to the associated severe morbidity and – at least for many patients with more severe disease – unsatisfactory treatment options available, research on IBD pathogenesis and factors triggering disease flares is currently intense. In addition, IBD has become a "prototype disease group" for chronic autoinflammatory disorders with a polygenic background and important multifaceted, environmental triggers.

There is clear evidence that environmental factors must contribute to both disease pathogenesis and disease flares [17–20]. The genetic risk factors have not changed over hundreds or thousands of years, but the disease incidence

#### Author contributions

All authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the conception, design, data interpretation and writing of the manuscript. The final version of the manuscript was approved by all authors.

#### Correspondence:

Gerhard Rogler, MD, Department of Gastroenterology and Hepatology, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, gerhard.rogler[at]usz.ch

and prevalence is still increasing as outlined above. Almost absent as a disease until 100 years ago, IBD now affects millions, including non-Caucasians, in whom the disease had been exceedingly rare – clearly indicating environmental influences. These environmental factors may either directly affect the gut or may mediate their effects via the intestinal microbiota [18]. Those effects may not only be immediate and direct. Epigenetic changes, for instance, may impact the intestinal ecosystem months and years after the environmental influence that caused the epigenetic alterations was present. But classical environmental factors, such as exposure to antibiotics with regards to microbial composition, may also exert an influence that is much more sustained than originally expected [21, 22].

Thus, IBD is a disease group par excellence from which to learn about the important interactions between genetics/genetic risk factors, environmental influences and “in-vi-environmental” factors, for example, the intestinal microbiota [18]. Despite the numerous genetic factors identified, it turns out that a limited number of main pathways are affected. Some of these important pathways will be discussed in the following paragraphs.

Pathophysiological insights obtained from IBD research are now being translated into other chronic inflammatory diseases such as arthritis, asthma or diabetes. This increases the value of results obtained in the IBD field. However, there are multiple gaps in our knowledge of the factors influencing disease progression and development of complications, which are responsible for a large part of the disease burden along the course of the diseases.

### What to learn from history: historical facts and their role for current pathophysiological concepts in IBD

Crohn's disease as a disease entity was described by Burrill B. Crohn, Leon Ginzburg and Gordon D. Oppenheimer in New York in 1932 as regional ileitis and later named after Crohn (an impressive example of how a surname's place in the alphabet may affect future recognition – at that time, alphabetic order determined positioning of co-authors) [23]. However, Crohn and colleagues were not the first to report this disease pattern: previous reports by other authors had been ignored or neglected in the medical-scientific community. This was described in detail by Crohn himself in the 1940s [24–26]. There were several reasons why Crohn's disease was named after Burrill B. Crohn on the basis of the above-mentioned publications, and the disease aroused medical-scientific interest. Some are still relevant for the disease concepts today.

In the 1920s, it became very popular to group patients with similar symptoms into disease entities and try to categorise symptoms. The concept of disease, as we know it today, evolved at the beginning of the 20th century. It became common to systematically record clinical symptoms that were similar and to define them as a syndrome or new disease. It was a transformation of the concept of disease, in which the enormous influence of the causal concepts of microbiology played a major role. The 1920s and 1930s were the heyday of microbiology. Many new diseases were based on the finding of a causative bacteria. Therefore, Burrill B. Crohn was initially convinced that regional ileitis or Crohn's disease was caused by a microbi-

ological agent, *Mycobacterium avium* subsp. *paratuberculosis* (MAP). Crohn's first manuscripts came to this conclusion by an analogy. He found that the so-called Johne's disease in cattle has many similarities with the human ileitis terminalis in terms of anatomical changes and histological findings. Based on these similarities and analogies, he concluded that both diseases – Johne's disease in cattle and regional ileitis in humans – must have the same trigger. In the context of the “microbiological revolution” mentioned above, it indeed was shown that MAP causes John's disease in cattle.

Despite unsuccessful attempts to detect *Mycobacterium avium* in patients with Crohn's disease, this hypothesis was maintained over the years and there is still a community of gastroenterologists that strongly believes in this pathophysiological hypothesis [27, 28]. The tissue of the terminal ileum of affected patients with Crohn's disease was homogenised and inoculated into guinea pigs or rabbits. Although this led to signs of disease of the respective species in other diseases with a microbiological, that is, bacterial, origin, there were no signs of disease in the animals for Crohn's disease. The experiment thus contradicted the infection hypothesis. Nevertheless, antibiotics were tested as a therapy for Crohn's disease and ulcerative colitis based on this hypothesis. And some of them proved to have some benefit for the patients.

The other reason why Crohn's description of the disease was picked up was its prevalence. At that time, its incidence and prevalence started to rise, so that many doctors had seen patients with similar symptoms. This indicates that indeed there was a change of (environmental) conditions that triggered disease onset in an increasing number of patients. MAP has been around for centuries. It is hard to believe that it would suddenly cause an “epidemic”. On the other hand, the genetic signature of the population has not changed within decades making a “gene” as the cause of those “new” diseases rather unlikely.

### The “immunological concept” of IBD pathology

The concept of autoimmune diseases was introduced into medicine 25 or 30 years ago. Immunology was one of the most successful biomedical sciences at that time [29–31]. According to the basic hypothesis, excessive or uncontrolled activation of the adaptive immune system (e.g., T cells and B cells) can lead to uncontrolled and chronic inflammation. Numerous publications deal with T cell subpopulations and adaptive immunity in chronic inflammatory bowel diseases [32–34]. The role of T cells has been studied extensively in animal models. The absence of regulatory T cells (FoxP3 positive cells) leads to the onset of colitis [35–37]. This led to concepts that suggest the adoptive transfer of regulatory T cells in patients with severe and refractory IBD [35]. In addition, it is well known that colitis can be induced via T cell costimulatory molecules [38, 39]. The activation of T cells is used in cancer therapy today (e.g., anti-CTLA4 antibodies, ipilimumab or programmed cell death protein 1 [PD1] and programmed death-ligand 1 [PDL-1] antibodies such as nivolumab and pembrolizumab) [40]. An important side effect of such therapies is the induction of “immune-mediated colitis” in melanoma or adenocarcinoma patients [41–43]. To some

extent, this is proof of the concept that adaptive immune cells contribute to the pathogenesis of IBD. Therapeutic principles that are established in IBD (such as systemic steroids and anti-tumour necrosis factor antibodies such as infliximab) are now successfully used to treat this immune-mediated colitis [44–47]. Interestingly, whether or not a patient will develop immune-mediated colitis as a side effect of tumour therapy seems to be dependent on the composition of the intestinal microbiota [48]. This points to an important role of the microbiota composition in the local activation of mucosal T cells – an aspect of IBD pathophysiology that will be discussed in more detail later.

T cells usually do not proliferate in the mucosa. They invade from the circulation to contribute to mucosal inflammation. Insights into the pathophysiological role of T cells, generated the idea to inhibit their migration to the site of tissue inflammation. Vedolizumab specifically inhibits the interaction between alpha4/beta7 integrin on lymphocytes and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM), which is almost exclusively expressed on endothelial cells in the gut. This approach has now been successfully introduced into clinical routine [49–53].

IBD is no longer seen as a classic autoimmune disease because most likely the antigens against which the adaptive immune system is primed originate from the intestinal microbiota. Furthermore, “autoimmune disease” implies an over-reactive, hyper-stimulated immune system, whereas rather the opposite appears to be a primary factor in the pathogenesis of IBD. Several of the hitherto established IBD risk single nucleotide polymorphisms code for genes involved in microbial defence (see below). The latter, in conjunction with the increase of microbes in the deeper layer of the mucus directly above the mucosal layer or even having penetrated the mucosal barrier in patients with IBD, indicates that activation in inflammatory pathways rather represents a secondary response due to initially impaired defence mechanisms. Nevertheless, the autoimmune disease concept has generated important insights that led to improvements of therapy.

### Genetic factors contributing to IBD pathogenesis

In older twin pair studies, 40 to 50% concordance of Crohn’s disease has been observed [54, 55]. The fact that even monozygotic twins have a concordance of less than 50% again indicates the important role of environmental factors in IBD pathogenesis. On the other hand, it clearly shows that genetic risk factors have an important role in disease onset. With the technique of genome-wide association studies (GWAS), those genetic risk factors could be detected. The first genetic risk factor identified to contribute to Crohn’s disease were variants in the nucleotide-binding oligomerisation domain protein 2 (NOD2) DNA in 2001 [56–59]. NOD2 is a pattern recognition receptor mainly expressed in cells of the innate immune system as well as in intestinal epithelial cells, binding muramyl dipeptide, which is a component of the bacterial cell wall. NOD2 variants that are associated with increased susceptibility to develop Crohn’s disease show impaired or deficient recognition of these bacterial wall products, again pointing to the importance of the microbiota for the pathogenesis of IBD. In the meantime, more than 250 genetic

risk factor have been identified [60, 61]. There are many shared genetic risk factors with other autoinflammatory diseases, such as lupus erythematosus, rheumatoid arthritis, psoriasis or type I diabetes [60]. There is also a large overlap between ulcerative colitis and Crohn’s disease with respect to genetic risk factors. This tells us that, based on the same genetic risk profile of an individual, different diseases may finally develop – again pointing to an additional role of environmental factors. The risk increases (odds ratios) associated with many of those genetic variants are only 1.2, meaning that the chance to get the disease is only 20% higher than normal having such a risk factors. In addition, it usually means that many healthy people or at least persons who are not affected by the specific diseases carry such risk factors. This is the reason why determining genetic risk factors cannot be used for diagnosis or even disease risk estimation. We learned a great deal about the pathophysiological pathways involved from genetic findings. However, the whole effort so far has not translated into clinical developments.

Nevertheless, the concept of risk genes has spread to the population. 23andme is the story of a great commercial success (“Find out what your DNA says about you and your family”) on a very dubious ethical and scientific basis.

### A crucial role for environmental factors in the pathogenesis of IBD

There is abundant evidence that in IBD, as in other chronic inflammatory diseases, environmental factors play an important role, for both disease onset and disease course (onset and duration of disease flares) [17–19, 62–64]. The risk of developing IBD and the subsequent disease behaviour in children of immigrants from low-incidence areas (Asia) coming to high-incidence areas (western Europe) is similar to that of the indigenous western population [65–67]. Living in an “urban environment” is a confirmed risk factor for IBD [68]. An increased prevalence of IBD in urban environments has been documented in Switzerland also [17]. It is obvious that research into these environmental factors causing or influencing IBD is important as, in contrast to the genetic risk factors, they can be changed or at least modulated. The prevention of environmentally triggered disease flares would be most relevant for IBD patients.

Unfortunately, reliable data on distinct environmental factors are limited. Only a few environmental factors influencing IBD disease course are unequivocally relevant [17]. Probably the best investigated environmental factor influencing IBD disease courses is smoking. Active smoking worsens the course of Crohn’s disease [69–73]. In Switzerland, twice as many patients with Crohn’s disease are active smokers compared with ulcerative colitis [74]. In striking contrast to the general population, significantly more women than men with Crohn’s disease smoke (42.8 vs 35.8%,  $p = 0.025$ ) [74]. Despite the well-established negative effects on the disease course, smoking rates in Crohn’s disease are alarmingly high, especially in female patients. Interestingly, smoking affects the colonic microbiota, providing a further link between the environment and the “in-vironment” [75, 76].



Other environmental factors that have been associated with clinical presentation or risk of inflammatory flares, as well as increased incidence, are diet and food additives [77–81]. Diet also may mediate its effects via the microbiota composition. Oral contraceptives and nonsteroidal anti-inflammatory drugs are the two main classes of frequently taken drugs that have been attributed to have potential to cause flares of the disease [17, 82–86].

Specific food additives such as titanium dioxide [87] or emulsifiers [77] also may contribute to the disease course as they impair the intestinal barrier function and allow bacteria to get into contact with intestinal epithelial cells that are normally protected by the mucosal mucus layer.

### The important role of the intestinal microbiota

The important role of the intestinal microbiota for the pathogenesis of IBD has been mentioned several times in other paragraphs. Evidence for a crucial role of the microbiota in IBD pathogenesis comes from several fields. In animal models of colitis, inflammation is prevented by germ-free conditions [88, 89]. Surgical diversion of the faecal stream is followed by improvement of inflammation in many patients with recurrence after restoration of the intestinal faecal stream [90, 91]. Several probiotics (such as *Escherichia coli* Nissle 1917) have shown efficacy in the treatment or the prophylaxis of flares in ulcerative colitis [92–94].

In addition, in recent years many authors confirmed an alteration of the intestinal microbiota in patients with IBD [95–101]. The changes found are generally referred to as “dysbiosis” or “reduced diversity”. It is unclear whether a reduction of specific bacterial strains such as *Faecalibacterium prausnitzii* is just an epiphenomenon or has indeed pathophysiological relevance. Unfortunately, most studies so far have analysed the microbiome with 16s-RNA gene sequencing. This allows only a rather crude estimation of the real changes occurring in the patients. In addition, the alterations are usually detected in patients with inflammation that itself may contribute to the observed changes.

The technique that has allowed the study of the intestinal microbiota composition is called high-throughput sequencing or pyrosequencing. It allows the analysis of 100,000 or 500,000 different DNA sequences of bacteria of the intestinal flora within a few hours. In order to process the obtained information, the latest computer technology is necessary.

The pathophysiological concepts, for Crohn’s disease at least, have now somehow returned to the point of origin. Now it is not a single bacterium that causes the disease as an infectious agent, but a dysbalance of the entire intestinal flora, which leads to an activation of the immune system. It appears that interesting disease concepts are never completely abandoned, but return in modifications.

### How epigenetic changes are involved in IBD pathogenesis

An important question has always puzzled investigators working on the pathogenesis of IBD: why is it possible that in Crohn’s disease the intestinal mucosa can be completely normal and healed for years and then the inflammation reappears at exactly the same location? Why can Crohn’s disease reoccur at a site where the involved area has been

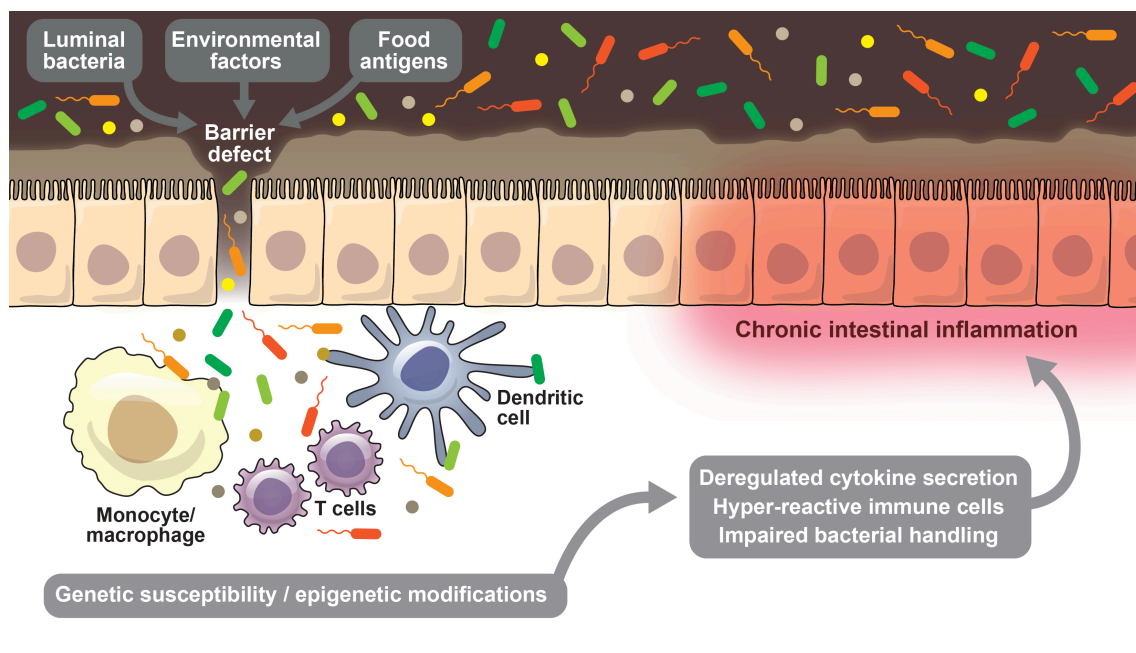
resected? How can a “disease memory” in the mucosa be explained? How can it happen that environmental influences act on the intestinal mucosa and the disease onsets years after this influence is gone (in the case of smoking)? The concept of epigenetic imprinting might give an answer to all these open questions and an explanation why there is a “disease memory” in certain areas of the gut wall. In fact, recent data provide significant evidence that epigenetic alterations also in healthy persons occur during lifetime. In patients with IBD, specific methylation patterns have been described [102–105]. Nimmo and co-workers reported a methylation profile that was found to be characteristic for Crohn’s disease of the terminal ileum [104]. In their analysis they found 1117 methylation sites to be differentially methylated, of which 50 showed significantly altered methylation in cases compared with controls [104]. There were distinct pathways that had an enrichment of differences in methylation that had been associated with the pathogenesis of IBD before, including genes relevant in the adaptive and innate immune system such as *MAPK13*, *FASLG*, *PRF1*, *S100A13*, *RIPK3* and *IL-21R* [104]. Interestingly, the authors also found a significant, 8.6-fold enrichment of methylation changes near GWAS loci of genetic risk factors of IBD [104]. Furthermore, certain complications such as fibrosis and strictures seem to be associated with a specific methylation pattern and subsequently with epigenetic modifications [102].

### Which common pathways may be important?

GWAS analyses and epigenetic profiling gave us insights into the genetic/epigenetic risk factors relevant in the pathogenesis of IBD. Many of them play a role in the recognition of and the response to the intestinal microbiota. In these defence pathways bacterial sensing, intestinal barrier regulating proteins and autophagy associated proteins, as well as cell stress and hypoxia stress response genes, play an important role [106–111]. Autophagy is an intracellular clearance system that leads to the degradation of intracellular debris such as misfolded proteins or invading bacteria [112]. Autophagy plays an important role in host defences against many bacteria, viruses and parasites [112] and for the maintenance of intestinal homeostasis. For many of the genetic variants and differentially methylated genes, however, the function and their role in IBD pathogenesis has not clearly been elucidated.

Interestingly some of the intracellular pathways in which the risk genes are involved are interconnected. Variants in the protein tyrosine phosphatase, non-receptor type 22 (PTPN22), for example, have been shown to be a risk factor for many autoinflammatory diseases such as IBD, rheumatoid arthritis, systemic lupus erythematosus or psoriasis. We recently demonstrated that this enzyme regulates NOD2-induced cytokine release, thereby modulating the response to the microbiota, as well as autophagy [113]. Further, PTPN22 controls the phosphorylation of NALP3, a protein of the inflammasome complex involved in interleukin-1 $\beta$  and interleukin-18 secretion and subsequently activation of the inflammasome [114, 115]. NALP3 itself has been identified to be a risk gene for Crohn’s disease. Another protein tyrosine phosphatase, PTPN2, also regulates the NLRP3 inflammasome (*Cell reports*, in press).

**Figure 1:** Current hypothesis of IBD pathogenesis. Intestinal microbiota, environmental factors and food antigens either cause a leaky barrier or penetrate through a barrier leak into deeper, submucosal tissue layers. In the genetically susceptible host, epigenetic modifications, and a dysregulation of the innate and adaptive immune response occurs. This finally manifests an intestinal inflammation.



Another interesting field in which pathways converge is the regulation of tissue pH. Tissue pH is altered by inflammation as well as during hypoxia. A G-protein coupled pH sensing receptor of the GPR4 family, TDAG8, also has been identified to be a risk variant for Crohn's disease in GWAS analyses. Hypoxia and inflammation are linked on many levels and influence each other [116]. Hypoxia also decreases the local pH in the mucosal tissue [117]. We recently reported that deletions of GPR4 or OGR1 protect from DSS induced colitis or ameliorates colitis in IL-10/pH receptor double knockout mice [118–120]. These pH receptors also are involved in the regulation of the intestinal barrier when activated [119]. Again we find a connection of the different pathophysiological relevant pathways in the mucosa such as stress response, hypoxia and autophagy [121].

Recently, we have seen first examples, that profound mechanistic and basic science investigations may not only improve our understanding on how and why IBD develops in a previous healthy human gut but also may directly support therapeutic decision making. For instance, an in-depth analysis of microbial composition and functional properties at baseline and during the administration of vedolizumab treatment in patients with IBD in conjunction with clinical data using sophisticated mathematical modelling revealed, that the functional microbial profile (including an increase in butyrate producing microbes in responding Crohn's disease patients) could be associated with therapeutic response.

Elucidating these critical pathways (summarised in fig. 1) and their role in IBD pathophysiology will help to develop new therapeutic targets and treatments in the future.

### Search strategy and selection criteria

References for this review were identified through searches of PubMed with the search terms “Crohn's disease, ul-

cerative colitis, pathophysiology”, from 1938 until September, 2017. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

### Disclosure statement

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